Medical and Clinical Research: Open Access

Research Article

The Impact of Cytotoxic T-lymphocyte Antigen-4 Genetic Polymorphisms on the Effectiveness of Ipilimumab and Patients' Outcome in Melanoma

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Received: July 11, 2022; **Accepted:** August 14, 2022; **Published:** August 19, 2022

Citation: Mohamed S. Omer, Peter S. Kanjo, Abuzar Elkhazeen, et al. The Impact of Cytotoxic T-lymphocyte Antigen-4 Genetic Polymorphisms on the Effectiveness of Ipilimumab and Patients' Outcome in Melanoma. Med Clin Res Open Access. 2022; 3(1):1-3.

ABSTRACT

Precision medicine is shaping the way medicine is being practiced, pharmacogenomics is the centerpiece of precision medicine. As in several fields, researchers are investigating the role of pharmacogenomic tests in the treatment of melanoma. One of these efforts is the ongoing preclinical and clinical trials investigating the impact of the genetic polymorphism of cytotoxic T-lymphocyte antigen-4 on drugs used in melanoma treatment. This paper reviews ipilimumab as a promising treatment for melanoma and how pharmacogenomic tests can substantially impact utilizing this drug in the treatment plan, whether as a solo treatment or in conjugation with other therapies. In this review, various databases and electronic libraries were utilized to search for and review different journal articles and papers about pharmacogenomic tests for ipilimumab. Although some results showed a minimal effect, most of the results revealed that pharmacogenomic tests for ipilimumab could play a crucial role in patients' outcomes. Further clinical trials are, however, needed on a larger scale to adopt this therapy in practice.

Keywords

Molecular Pathology, Pharmacology, Dermatology, Oncology, Melanoma.

Introduction

Due to increased access to the sequencing of human genes in recent times, researchers have started to analyze genes that code proteins that regulate the immune system. Among these genes is the cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene (known as CD152), which many researchers have focused on because of its pivotal role in cancer pathogenesis and autoimmunity [1]. After the activation of T lymphocyte cells, CTLA-4 is expressed on the T lymphocyte surface due to recycling intracellular storage and new gene expression [2]. When the expressed CTLA-4 binds to its ligands, B7-1 and B7-2, it inhibits the activated T cells, which might lead to immune response termination and immune tolerance [2]. Studies have shown a significant association between CTLA-4 polymorphism and susceptibility to different cancers [2]. Polymorphisms that have been reported in the CTLA-4 gene include positions -138, -1661, - 1772, and +49, and in 3 prime untranslated regions at position +6230, known generally as CT60 [1].

Blocking of the CTLA-4 gene with anti-CTLA-4 antibodies is currently being used as a treatment approach for metastatic melanoma, driven by promoting and increasing antitumor T cell expansion expression activation [2]. Ipilimumab is the first drug

of this kind approved by the FDA that is designed to target the human CTLA-4 T cell protein. Several studies have shown that patients treated with anti-CTLA-4 antibody after long-term follow-up, ipilimumab has an extraordinary potential to induce long-term protection against cancer relapse [3]. Other studies have also demonstrated increased overall survival in patients with advanced melanoma treated with ipilimumab [3]. Further, ipilimumab improved overall survival in metastatic melanoma: the median survival following the use of the drug alone was 10.1 months [4]. Only 5%–10% of patients treated with anti-CTLA-4 therapy show response [1].

New criteria, such as immune-related response criteria, have been suggested to evaluate the clinical responses more accurately. This review investigated how genetic polymorphism of the targeted gene CTLA-4 affects the efficacy and outcome of the monoclonal antibody ipilimumab in patients with melanoma.

Background

In April 2013, the Human Genome Project uncovered around 20,500 genes with a human-to-human genetic variation of 0.5%, while 99.5% of the human genes were similar [5]. The most widely recognized type of DNA sequence variation is the single nucleotide polymorphism (SNP) [5]. Other types of variation include deletions, insertions, tandem repeats, inversions, and copy number variations. Collectively, these are called structural variations. SNPs and structural variations serve as biomarkers and determine a person's reaction to specific medications and environmental factors, as well as the risk of developing a disease. Therefore, the recent precision medicine initiatives proposed in 2015 paved the way to utilizing these data to improve the healthcare system. Since then, efforts have been made to integrate pharmacogenomics and pharmacogenetics into the healthcare system. Pharmacogenomics involves studying the connection between genomic variations and their impact on drugs, while pharmacogenetics concerns investigating the impact of a single gene on drug reactions. Both pharmacogenomics and pharmacogenetics are connected to drug metabolism, which impacts drug efficacy and safety at a given therapeutic dose.

Pharmacogenetic tests have been incorporated into various treatment plans for cutaneous tumors, including melanoma. Melanoma is a type of skin tumor that arises from melanocytes—the cells that give the skin its pigmentation [6]. There are many therapeutic approaches for the treatment of melanoma. Some of the approaches target BRAF V600E/K, while others target mitogen- activated protein kinase. Another group of drugs called monoclonal antibodies targets PD-1 and CTLA-4, such as ipilimumab [7]. Ipilimumab is the only licensed anti-CTLA-4 antibody and has shown promising outcomes with Phases 3 and 4 unresectable melanoma—especially in combination with anti-PD-1, such as nivolumab [8].

This review is focused on ipilimumab and its mechanism of action. To understand how ipilimumab works, an explanation of the effect of cytotoxic T-helper cells in melanoma is needed. The human CTLA-4 or CD152 gene is found on chromosome number 2; it is approximately 6.2 kb and consists of 4 exons [1]. CTLA-4 (CD152) gene belongs to the super immunoglobulin family and plays an essential role in the human immune system, specifically in downregulating T-cell activation and effectiveness [6]. T cells are immune cells that control the immune response and constitute T helper cells (Th), which are part of the regulatory cells that identify pathogens from other cells and cytotoxic T lymphocyte cells that attack antigens.

Recently, various pharmacogenetic tests for ipilimumab were released, and this contributed to the increase in its clinical utility and efficacy and a reduction of its side effects. This literature sheds light on some of these tests.

Material and Methods

A literature search and reviews were conducted utilizing literature screening through different research websites, including PubMed, Google, HUGO Gene Nomenclature Committee database, the Ohio State University library website, and the Online Mendelian Inheritance in Man website.

Results

Queirolo P, et al.'s study investigated the link between the variants of the CTLA-4 gene, the response to ipilimumab, and the long-term survival of patients with metastatic melanoma treated with ipilimumab [9]. The authors enrolled 173 patients with metastatic melanoma from July 2010 to November 2013. Then, they analyzed the genotype and the frequencies of CTLA-4 variants in these patients and 100 control subjects. They were six CTLA-4 single nucleotide variants (SNVs) and each had three genotypes: G/G, G/A, and A/A. Of the 173 patients, 20.8% showed partial response or complete response, 9.2% showed stable disease, while 69.9% showed progressive disease.

The authors found that patients showed a similar frequency of immune-related partial response regardless of the genotypes for both −1577G>A and CT60G>A SNVs. In contrast, G/G carriers presented a higher rate of immune-related partial response and/or immune-related complete response as opposed to the A/A carriers, which were linked to an increased rate of immune- related stable disease. The G/A carriers demonstrated an intermediate frequency of both immune-related partial response and/or immune-related complete response [9].

Utilizing logistic regression analysis, the investigators detected a decrease in the percentage of the progressive and responder patients as the dose of allele A increased. In comparison with G/G, G/A showed a probability of immune-related partial response and/or immune-related complete response. Utilizing the same modeling restrictions, a similar result with allele A "dose" was also detected for immune-related progressive disease versus immune-related stable disease comparison [9].

Discussion

Queirolo P, et al.'s study hypothesis assumed that since CTLA-4 is a key deregulator of the activation of T cells, variations in genetics that alter the expression and/or function of this gene could affect the gene's interaction with ipilimumab and, thus, the clinical outcome of these patients. Evidence has shown a possible effect of the -1577G>A and CT60G>A SNVs to favor overall survival and success in therapies through blocking the CTLA-4 gene [9]. This study confirms that the CTLA-4 -1577G>A and CT60G>A variants are associated significantly with the best overall response to treatment with ipilimumab.

Logistic regression analysis of the best overall response indicated a strong decreasing tendency in the relative frequency of responder/progressive patients compared to stable patients, implying that patients harboring the A allele seem to induce an effect on the stability of the disease [9]. Approximately, 70% statistically significant reduction for G/A versus G/G and about 95% for A/A versus G/G were observed.

In Breunis et al.'s study, 152 patients with melanoma were treated with CTLA-4 antibody through genotyping of five CTLA-4 tag SNPs plus two SNPs in the 3 prime untranslated region of the gene. Of these, 23 (15.1%) showed response to therapy, and 18 out of the 48 patients that developed stage III/IV autoimmune toxicity were responders [10].

Preliminary evidence has indicated an association with three correlated SNPs and two CTLA-4 haplotypes with response to ipilimumab. In vitro experiments showed that the A allele is associated with a significant expression on the cell surface than the G allele [10]. This association provides evidence of the functional importance of polymorphism and might have caused the observed association. Alternatively, it can also be explained by the fact that SNP is in linkage disequilibrium with an untested CTLA-4 polymorphism and could be functionally important.

Conclusion

The results of these studies and other similar studies connecting genetics to clinical outcomes are promising. With the increasing number of drugs available for the treatment of melanoma, precision medicine can be a valuable tool to provide the most effective treatment for patients such as -1577G>A and CT60G>A CTLA-4 variants might accurately predict the effectiveness of ipilimumab therapy for patients with melanoma.

Nevertheless, definitive conclusions about the significance of genetics to the clinical outcome of patients with melanoma treated with ipilimumab require further investigation. Also, the results of these studies need to be validated in large clinical randomized trials, comparing patients with similar clinical characteristics treated with and without ipilimumab. Furthermore, it is important to note that some of these CTLA-4 variants did not show any significant effect in patients with melanoma treated with adjuvant interferon-alpha therapy [10]. This supports the hypothesis that determined that SNVs are involved in CTLA-4-based immunotherapy.

Therefore, if further investigations confirm these associations and the functional consequences of the associated variants, it will be essential to test common genetic variants in CTLA-4 that are responsible for the difference in treatment outcomes amongst patients with melanoma.

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